REMARKS

Claims 15-17 and 25 are pending in the present application. Reconsideration and withdrawal of the rejections are requested in view of the amendments.

The Rejection Under 35 U.S.C. §112, Second Paragraph, Should be Withdrawn

The rejection of claims 15 and 16 under 35 U.S.C. §112, second paragraph, has been maintained. The rejection is respectfully traversed for the reasons described below.

The Examiner argues that the term "solvates" was included in the scope of the previous rejection in the Office Action mailed February 28, 2008. It is noted that in the previous Office Action, the Examiner stated that the rejected claims were indefinite because, "it is unclear [] which derivatives are being claimed." Applicants construed this sentence to suggest that only the phrase "physiologically functional derivatives" was covered by the rejection. With respect to solvates, the specification provides guidance regarding the meaning of this term as well as examples of solvents that may be used to create such solvates. See, for example, line 26 of page 12 through line 2 of page 13. Accordingly, one of skill in the art, when reading claims 15 and 16 in light of the supporting specification, would be able to ascertain the scope these claims.

In view of the above remarks, all grounds for rejection under 35 U.S.C. §112, second paragraph have been overcome. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

The Rejection under 35 U.S.C. §103(a) Should be Withdrawn

The rejection of claims 15-17 and 25 under 35 U.S.C. §103(a) on the grounds that they are unpatentable over Boloor *et al.* (WO02059110) and Ciardiello *et al.* in view of Rusnak *et al.* has been maintained. The rejection is respectfully traversed for the reasons described below.

In the Office Action, it is again argued that it would be *prima facie* obvious to one of ordinary skill in the art to treat cancer with GW2016 (taught by Rusnak *et al.*)

in combination with a compound of Formula I because both compounds were known in the art to be capable of treating cancer, and because chemotherapeutic combinations are well known in the art. In the amendment dated August 27, 2008, the applicants demonstrated that:

(1) While one of ordinary skill in the art might be motivated to test various combinations of anti-cancer agents in a method of treating cancer, it is not possible to predict *a priori* which combinations will be beneficial to patients. Therefore, there is no reasonable expectation that a particular combination will be beneficial until it is tested.

(2) Even if the Office Action had established a *prima facie* showing of obviousness for the invention recited in claims 15-17 and 25, there is sufficient evidence to rebut such a showing. Preliminary results of a recent clinical trial demonstrate that treatment of breast cancer with a reduced dose of lapatinib (1000 mg/day) combined with pazopanib at 400 mg/day offers therapeutic advantages when compared with treatment with a higher dose (1500 mg per day) of lapatinib alone.

In the Final Office Action, neither of these lines of argument are substantively addressed. With regards to the first line of argument, the Examiner cites Beers *et al.* (Reference 1 on the Form PTO-1449 submitted on August 27, 2008) for the teaching that "the rationale for combination chemotherapy is to use drugs that work on different parts of the cancer cell's life cycle." However, the applicants have not argued that combination cancer therapy is not well known in the art. Rather, the applicants have shown that the therapeutic effects of a particular combination cannot be predicted *a priori*. As a result of the unpredictability, there can be no reasonable expectation that a particular combination will show benefits for a patient until that combination has been tested. The Examiner states, "Applicant has failed to provide representative set of comparisons of similar types of agents in support of their arguments. Applicant's representative have simply 'pick and choose' different agents, many of which have varying mechanisms of actions from the agents claimed." It is unclear to the applicants what additional comparisons the Examiner

believes are necessary to support the applicants' argument. The applicants have already provided references documenting four separate instances in which chemotherapeutic combinations of agents acting in different parts of the cancer pathway showed no benefit in comparison with treatment by the single agents comprising these combinations. Further clarification regarding the Examiner's request for additional comparisons is respectfully requested.

With regards to the second line of argument, the Examiner states, "the Applicants have not set forth any reason why the results in fact render the invention unobvious." The applicants respectfully disagree with this conclusion. The applicants have presented evidence that the benefits of any particular cancer treatment combination are unpredictable until that combination is tested, and that in some instances combination therapy offers no advantage in comparison with monotherapy with the single agents comprising the combination. The applicants have further shown that in a phase II trial in which breast cancer patients were treated with either GW2016 (lapatinib) alone at a dose of 1500 mg per day or a combination of a lower dose of lapatinib (1000 mg per day) and a compound of Formula (I) (pazopanib; 400 mg per day), the response rate at week 12 was 44.9% with the combination and 28.8% with the lapatinib monotherapy according to the investigator's assessment, and 36.2% with the combination and 22.2% with the monotherapy according to an independent assessment. In addition, patients treated with the combination showed an improved rate of progression-free survival during the 12-week treatment period in comparison with patients treated with lapatinib monotherapy. Because the benefits of combination therapy cannot be predicted *a priori*, the advantages of the lapatinib/pazopanib combination in treating breast cancer in comparison with lapatinib monotherapy at a higher dose could not have been anticipated. Accordingly, the use of this combination in the treatment of breast cancer is non-obvious.

In view of the above arguments, all grounds for rejection under 35 U.S.C. §103 have been overcome. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

Applicants believe that all claims are in condition for allowance and such action is respectfully requested. Applicants believe that no other fees are due in connection with the filing of this paper other than those specifically authorized herewith.

Should any other fees be deemed necessary to effect the timely filing of this paper, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 07-1392. If the Examiner has any outstanding issues with the pending claims, she is encouraged to telephone the undersigned at (919) 483-1467 for expeditious handling.

Respectfully submitted,

Kathryn L. Coulter

Kathryn L. Coulter
Attorney for Applicant
Registration No. 45,889

Date: 1/6/2009

Customer No. 23347
GlaxoSmithKline
Corporate Intellectual Property
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709-3398
Telephone: (919) 483-1467
Facsimile: (919) 483-7988